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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/108,673	07/01/98	TENG	C ISIS-3105

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	32

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/108,673	Teng et al
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 6, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *25-27, 40, 44-50, 53-64, and 66-81* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-27, 40, 44-50, 53-64, and 66-81* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☒ Interview Summary (PTO-413) Paper No(s). *32 & 33*

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Response to Arguments

1. In response to the telephonic interviews of July 12, 2001 and September 6, 2001, the prosecution of this application is hereby reopened to amend the rejection of the claims under 35 USC 103 to clarify the point of combination of two references to make obvious the two fatty acids in the composition of claim 44, and the methods claims dependent thereon.

2. The rejections and objections set forth in the Final Office Action, mailed June 15, 2001 are repeated below, with the exception of the rejection of the claims under 35 USC 103 as discussed above.

3. As stated in the interview summary of July 12, 2001, the definition of the term "fatty acid' has been narrowly construed to mean only a true "fatty acid" and does not include modified "fatty acids" such as fatty acid esters.

Claim Objections

4. Claims 54 and 76 are objected to because of the following informalities: Typographical errors occur in the claims. Claims 54 and 76 contain the word "proylene" which should be "polyethylene". Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 25-27, 40 and 66-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of use of a composition containing nucleic acid in an animal. The specification is directed to a method of treating and a method of investigating the role of a gene or gene product in an animal having or suspected of having a disease or disorder that is treatable in whole or in part with one or more nucleic acids delivered to the animal via the enteral route.

The Specification does not teach one of ordinary skill in the art how to treat or investigate the role of a gene or gene product in an animal (which may be other than a human). Treatment with nucleic acids is a new and developing art involving gene therapy which is highly unpredictable. While the Specification does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway which is a step toward a pharmaceutical treatment with nucleic acids, it does not teach one of ordinary skill in the art how to treat nor investigate a role of a gene or gene product with nucleic acids since the

practice of the treatment or investigation is highly unpredictable, and would require specific teachings to guide the ordinary skilled artisan how to make and use the claimed invention. As such, specific teachings must be present in the Specification to support any claims to treatment or investigation in an animal with a nucleic acid. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivery via the enteral route of a nucleic acid to an animal and treating the animal with the nucleic acid. Treatment of an animal with a nucleic acid is a new and developing art, and as such requires detailed teachings on how to make and use such a nucleic acid.

b- The specification teaches the delivery of a nucleic acid via the enteral route to the blood and generally into the internal organs of an animal by cannula delivery of nucleic acids to the small intestine of a rat. There are no teachings of treatment with the nucleic acid.

c- The nature of the invention is complex. Treatment of animals with nucleic acids is a new and developing art as taught in Gewirtz et al. (see the entire article). Gewirtz et al. taught the difficulties of therapy with nucleic acids such as antisense oligodeoxynucleotide, stating that there are two major problems which must be overcome. First, the nucleic acid must find its

cellular target. Second, it must then find and act on its intracellular target. The specification does not teach one of ordinary skill in the art how to direct the nucleic acid to its cellular target nor how the nucleic acid would then act on its intracellular target.

d- The state of the prior art as taught by Gura (see especially page 575, column 1, second paragraph, and page 576, third paragraph to the end of the article) demonstrates some of the difficulties associated with nucleic acid pharmaceutical therapy, stating "[b]ut the biggest concern is that antisense compounds simply don't work the way researchers once thought they did"...."Besides not always working by 'true antisense mechanisms,' the synthetic oligonucleotides have also caused side effects in experimental animals."

e- The state of the art as recited in Stull et al. (see especially pages 476-478) taught that the stability, affinity, efficiency and subcellular distribution of the nucleic acids in the host animal are all areas of uncertainty and need careful study and analysis before any nucleic acid therapeutic modality can be understood and consistently applied. Also, Agrawal et al. taught the delivery of synthetically modified nucleic acids administered to rats via the oral route. However, the nucleic acids had been specifically modified to resist nuclease digestion. Also, no pharmaceutical therapy was demonstrated by Agrawal et al.

f- The teaching of absorption into the blood and internal organs of the nucleic acids in the instant Specification does not demonstrate any targeting of the nucleic acid to a cell or to intracellular targets as recited by Gewirtz et al., nor does the Specification address any of the issues raised by Gura or Stull et al. Therefore, no pharmaceutical effect has been demonstrated.

g- For the reasons stated by Gewirtz et al., Gura, and Stull et al. the unpredictability of pharmaceutical applications of nucleic acids is very high.

h- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

7. In addition, claims 40, 50, 63 and 74 are not enabled because the claims recite that an antisense oligonucleotide "modulates" the expression of a cellular adhesion protein or the rate of cellular proliferation. The word "modulate" generally means to increase or decrease. An antisense nucleic acid molecule only causes a decrease in expression. Therefore, one of skill in the art would not know how to increase expression with an antisense molecule, and a method to increase expression is not taught in the instant specification.

Response to Arguments

8. Arguments set forth in Paper No. 28 assert that the invention is enabled. It is asserted that the Declaration of Drs. Teng and Hardee provides evidence that nucleic acid uptake across the intestinal mucosa is enhanced by the addition of the claimed compositions. Enablement for the full scope of the specification is required for enablement of the claims as written, and claims which recite the use of a nucleic acid must be enabled for all of the stated uses of the nucleic acid. As set forth above, the claims are not enabled for a gene therapy use of a nucleic acid.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 25-27, 56, 64, 78 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The claim is drawn to a method of enhancing penetration of a composition comprising a nucleic acid and at least two fatty acids across the alimentary canal of an animal. However, there are no method steps for administering the composition to the alimentary canal.

12. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 64 recites the broad recitation "chemical modification selected from the group consisting of a modified nucleobase, a modified sugar residue, and a modified backbone linkage", and the claim (base claim 61) also recites "chemical modification selected from the group consisting of cytosine to 5-methyl-cytosine substitution, a phophorothioate linkage and a 2'-methoxyethoxy modification" which is the narrower statement of the range/limitation.

13. Claim 66 recites the limitation "said oligonucleotide" in line 3. There is insufficient antecedent basis for this limitation in the claim.

14. Claims 56 and 78 recites the limitation "when administered to an animal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 80 recites "[t]he method of claim 66 wherein said composition comprises a bile salt". The claim should state "**further** comprises" (emphasis added) to eliminate confusion as to the metes and bounds of the claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 44-50 and 53-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/05903 (Watts et al., of record) in view of US 5,994,062 (Mulshine et al.) and US 5,707,648 (Yiv, of record).

WO 97/05903 taught (see the abstract, pages 2, 3, 5-8, 14 and the claims) a composition comprising a nucleic acid and a mixture of fatty acids (one fatty acid is taught to be capric acid, another is a salt of lauric acid), polyethylene glycol, bile salts and a carrier, where the oligonucleotide may be in a prodrug form. The composition may contain less than 8% water. The composition is used in a method to enhance the penetration of the nucleic acid across the alimentary canal of an animal.

WO 97/05903 did not teach that the oligonucleotide was modified.

US 5,994,062 taught (see especially the abstract, summary, columns 16-18) a method of delivery of a composition comprising a modified nucleic acid to the alimentary of an animal. The composition may contain penetration enhancers such as bile salts. US 5,994,062 taught the advantage of use of modified nucleic acids for the purpose of making the nucleic acids resistant to destruction in the animal.

US Pat No. 5,707, 648 taught (see especially the abstract, the summary, columns 3-8, 12-13 and the claims) a composition comprising fatty acids of C_{8-18}, an antisense oligonucleotide and a carrier compound. The composition may be water based (which may be less than 8%) or

propylene glycol based. The composition may have at least 15% bioavailability of the nucleic acid when administered to a mammal. The composition may contain a bile salt. The antisense oligonucleotide may be chemically modified.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the composition comprising a nucleic acid and a mixture of fatty acids , polyethylene glycol, bile salts and a carrier, where the oligonucleotide may be in a prodrug form, and the composition may contain less than 8% water, and where the composition is used in a method to enhance the penetration of the nucleic acid across the alimentary canal of an animal of WO 97/05903 with the method of delivery of a modified nucleic acid to the alimentary canal in a composition which may contain penetration enhancers such as bile salts to the alimentary canal of an animal of US 5,994,062 because US 5,994,062 taught the advantage of use of a composition comprising modified nucleic acids for the purpose of making the nucleic acids resistant to destruction in the animal, in a method of delivery of the composition to the alimentary canal of an animal. Both prior art references taught the delivery of nucleic acids across the alimentary canal of an animal, and both used penetration enhancers to enhance delivery of the nucleic acid to the animal. It therefore would have been prima facie obvious to one of ordinary skill in the art to use the penetration enhancers of WO 97/05903 which enhanced the delivery of nucleic acids with the modified, enzyme resistant nucleic acids of US 5,994,062 (with penetration enhancers) to enhance the delivery of nucleic acids across the alimentary canal of an animal. The combination of fatty acids taught by each of WO 97/05903 and US 5,707,648

make obvious the combination of two or more fatty acids in a composition as taught in the instant claimed composition and methods, since it is obvious to combine the teachings of two compositions and methods to make a third composition which is merely the combination of the two compositions, namely, two or more fatty acids in the instant composition.

One of ordinary skill in the art would have been motivated to combine the composition of WO 97/05903 with the method of delivery of US 5,994,062 because each of US 5,994,062 and WO 97/05903 taught a method of delivery of nucleic acids across the alimentary canal of an animal. WO 97/05903 taught the advantage of use of fatty acids and other penetration enhancers to deliver the nucleic acids, and US 5,994,062 taught the advantage of using modified nucleic acids which made the nucleic acids resistant to destruction in the animal. Both prior art references taught the delivery of nucleic acids across the alimentary canal of an animal, and both used penetration enhancers. Each prior art reference taught the advantageous use of penetration enhancers, and each taught the enhanced delivery of nucleic acids across the alimentary canal of an animal. The combination of fatty acids taught by each of WO 97/05903 and US 5,707,648 make obvious the combination of two or more fatty acids in a composition as taught in the instant claimed composition and methods, since it is obvious to combine the teachings of two compositions and methods to make a third composition which is merely the combination of the two compositions, namely, two or more fatty acids in the instant composition. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing

the instant claimed invention given the teachings of WO 97/05903, US 5,994,062 and US 5,707,648.

Conclusion

18. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Robert Schwartzman can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
October 16, 2001

TERRY MCKELVEY
PRIMARY EXAMINER